PREDICTING ADULT CHOLESTEROL LEVELS FROM MEASUREMENTS IN CHILDHOOD AND ADOLESCENCE: THE MUSCATINE STUDY*

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ADVERSE EFFECTS of elevated blood cholesterol levels have been established by longitudinal observation of adult populations observed at middle age and followed until morbidity and mortality result from arteriosclerotic disease.[1-6] In addition, adult men with elevated cholesterol levels have been shown to benefit by lowering their levels of cholesterol utilizing diet and bile acid sequestrant therapy.[7] Many studies have described tracking of cholesterol levels during childhood and adult life,[8-12] but few children[13] have had their cholesterol levels measured and been followed for many years to observe the predictive value of childhood measurements to adult coronary artery disease risk levels.

In this study longitudinal observations of a population first measured during childhood at ages eight to 18 years and reexamined more than a decade later when their ages ranged from 20 to 30 years are presented. Observations indicate that elevated levels of cholesterol during childhood are associated

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with a higher risk for elevation in adult life. In addition, obesity acquired during adolescence and young adult life, oral contraceptive use, and cigarette smoking have deleterious effects upon adult cholesterol and its fractions.

POPULATION AND METHODS

From 1971 to 1985, on alternative years, the school children of Muscatine, Iowa, were surveyed for height, weight, triceps skinfold thickness, blood pressure, plasma cholesterol, and triglyceride. These children were in kindergarten through the 12th grade. Beginning in 1981, those previously measured during their school age were recalled for examination at ages ranging from 20 to 30 years. In all, 3,891 individuals were eligible in the study. We were able to locate 90% of these. Fifty were dead. For the purpose of this study, 20 nonwhite adult subjects, 18 diabetic, and 22 taking lipid-lowering drugs were excluded. Of those excluded, mean childhood measures did not differ from their age and gender matched peers. After these exclusions, we were able to obtain blood samples and questionnaire data on 2,446 (67% of those who were eligible). Table I shows the number of adults examined by age range and gender.

Many individuals in the longitudinal cohort were measured more than once during their school years. Table II shows the average time between childhood and adult examinations and the number of observations made in the 2,446 subjects in the longitudinal cohort.

At the time of recall, the adult subjects had the following measurements: height, weight, triceps skinfold thickness, three right-arm seated random-zero blood pressures (the average of these are used herein), fasting plasma cholesterol, HDL-cholesterol, and triglyceride levels. For both children and adults, the Quetelet Index (weight/height^2) was calculated and is presented as a measure of ponderosity. In addition, these adult subjects completed a questionnaire about the use of thyroid, lipid-lowering, oral contraceptives and other medications. The use of tobacco and alcohol as well as exercise habits at work and at home and socioeconomic status were ascertained. We also determined by questionnaire whether the subjects had a family history of high cholesterol levels, hypertension, myocardial infarction, stroke, or diabetes. Family history was defined as positive if the subjects' parents or siblings had experienced the abnormality.

The methods of examination during the school-age years have previously been described.[9,14] The training and certification of the examiners for the adult measurements were the same as those described by the Lipid Research Clinics.[7,15] The laboratory methods for the measurement of total cholesterol,

TABLE I. NUMBERS OF YOUNG ADULTS IN THE LONGITUDINAL COHORT

Adult age (years)	*Females*	*Males*	*Total*
20–25	750	677	1,427
26–30	529	490	1,019
Total	1,279	1,167	2,446

TABLE II. LENGTH OF FOLLOW-UP AND NUMBERS OF CHILDHOOD OBSERVATIONS ON THE LONGITUDINAL COHORT

	Adults 20–25 (years)			*Adults 26–30 (years)*		
Childhood age (years)	*Average length of follow-up (years)*	*Numbers of childhood observations*		*Average length of follow-up (years)*	*Numbers of childhood observations*	
		Females	*Males*		*Females*	*Males*
7–8	15	54	55	—	—	—
9–10	13	311	292	—	—	—
11–12	12	542	476	—	—	—
13–14	10	551	490	14	184	155
15–16	8	415	352	12	305	263
17–18	6	316	299	11	246	233

HDL-cholesterol, triglycerides, and the calculation of LDL-cholesterol were also the same as the Lipid Research Clinic protocol.[16] The laboratory carrying out the lipid analyses for both the childhood and adult levels was the Iowa Lipid Research Clinic Laboratory, which participated in the Communicable Disease Center Laboratory standardization program. Throughout the study samples sent for comparative analyses from the center deviated no more than ±3% from the mean of the standards.

To determine whether those subjects who participated in the adult surveys differed significantly from the population that participated in any school survey, all childhood observations were converted to age-gender-survey year specific Z-scores [Z=(observed value−mean)/standard deviation, where the means and standard deviations were computed independently for each year of age, gender, and survey year]. All mean Z-scores were not significantly different than zero except for height, which was only 0.05 standard deviations (approximately 0.5 cm) greater than the mean of all school-age participants. These observations indicate that those subjects examined longitudinally represented the initial sample of the children with little bias.

Statistical methods. Adults were targeted for measurement at their 24th or 28th birthday and most were sampled within six months of these ages. For this paper we categorized adult age into two discrete intervals, 20 to 25 years

and 26 to 30 years. Childhood surveys were carried out every other year so that a child was measured only once in any two-year age interval. Many children were measured several times; however, only one observation on a child was used in any two-year age category in the analyses performed.

All continuous variables were examined for normality. Those not normally distributed were transformed using the log transformation and both raw and transformed data were analyzed. Conclusions from analyses of transformed and untransformed variables always agreed. Only results for the untransformed data were reported, but if a variable was not normally distributed, then the log transformed variable was used in Pearson correlations.

Cholesterol percentiles were calculated for each adult age-gender group, and dichotomized into those less than the 90th percentile for age and gender and those equal to or greater than the 90th percentile. Logistic regression was used to estimate the risk (probability) that adult levels would reach or exceed the 90th percentile. Analysis of variance was used to examine the effects of tobacco and alcohol use on adult lipid levels. Student's t-tests were used to determine the effects of oral contraceptive use on lipid levels.

Stepwise linear regression was used to quantify the percent of explained variability in adult cholesterol contributed by childhood cholesterol, change in Quetelet Index, and oral contraceptive use. These analyses also included adult alcohol use, tobacco use, exercise habits, socioeconomic status and triceps skinfold thickness as predictor variables. These latter variables never contributed significantly and do not appear in the summary of results.

RESULTS

Correlations of childhood with adult levels. Pearson correlations of the childhood age-gender-specific levels of total cholesterol with the adult levels of total cholesterol, LDL-cholesterol, HDL-cholesterol and LDL/HDL cholesterol ratios are presented in Table III. This table also shows the correlation of childhood with adult Quetelet Index and change in cholesterol with change in Quetelet Index from childhood to adulthood. These data indicate a relatively high degree of consistency of peer rank order of the population levels of cholesterol and Quetelet Index from childhood to adult life. They also show that total cholesterol measurements in childhood are predictors of adult LDL-cholesterol levels and LDL/HDL ratios, but not adult HDL-cholesterol. Changes in Quetelet Index are related to important adverse changes in cholesterol levels.

Risk of elevated levels at adult age. The risk (probability) of having a plasma total cholesterol level in the upper decile of the adult distribution is shown in Figure 1. Data presented show the risks by interval of childhood

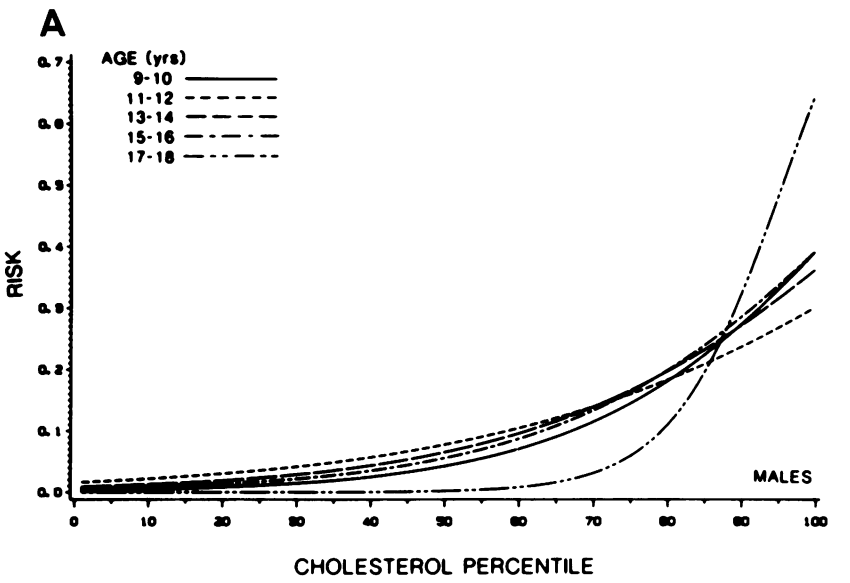
TABLE III. CORRELATIONS* OF CHILDHOOD WITH ADULT LEVELS

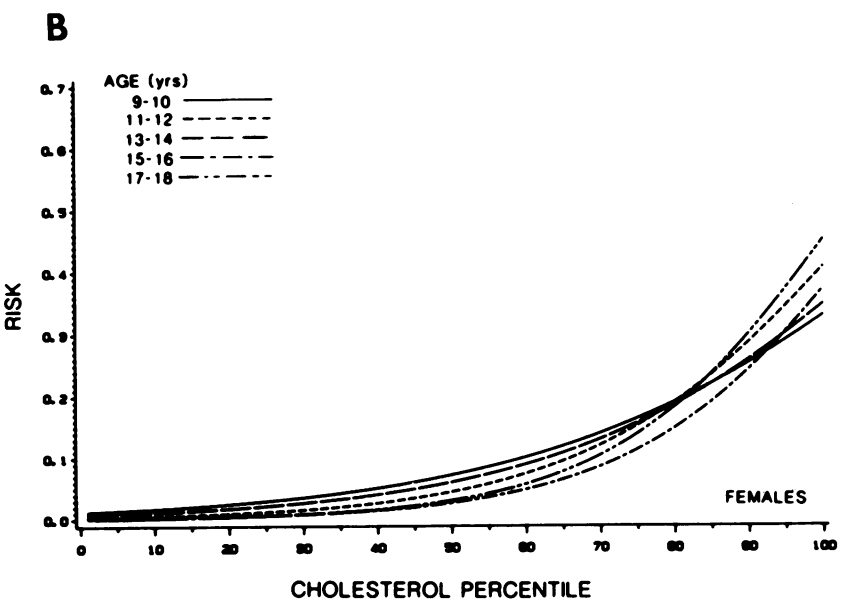
Childhood age (years)		*7–8*	*9–10*	*11–12*	*13–14*	*15–16*	*17–18*
Adult age (years)							
				Childhood cholesterol with adult cholesterol			
20–25	Female	0.64	0.49	0.54	0.52	0.53	0.54
	Male	0.56	0.58	0.51	0.51	0.64	0.72
26–30	Female				0.52	0.55	0.48
	Male				0.52	0.63	0.64
				Childhood cholesterol with adult LDL-cholesterol			
20–25	Female	0.65	0.47	0.53	0.49	0.49	0.56
	Male	0.56	0.56	0.47	0.47	0.60	0.63
26–30	Female				0.49	0.50	0.45
	Male				0.50	0.56	0.61
				Childhood cholesterol with adult HDL-cholesterol			
20–25	Female	−0.25+	0.01+	0.06+	0.11	0.15	0.13+
	Male	0.07+	0.07+	−0.04+	−0.02+	−0.03+	−0.07+
26–30	Female				0.08+	0.10+	0.04+
	Male				0.16+	0.06+	0.06+
				Childhood cholesterol with adult LDL/HDL ratio			
20–25	Female	0.61	0.30	0.32	0.25	0.24	0.32
	Male	0.38	0.41	0.33	0.33	0.44	0.46
26–30	Female				0.25	0.29	0.29
	Male				0.28	0.39	0.42
				Childhood quetelet index with adult quetelet index			
20–25	Female	0.53	0.60	0.66	0.69	0.74	0.72
	Male	0.60	0.68	0.69	0.71	0.77	0.81
26–30	Female				0.71	0.68	0.67
	Male				0.84	0.70	0.78
				Change in cholesterol with change in quetelet index			
20–25	Female	0.21+	0.06+	0.10	0.09	0.15	0.23
	Male	0.36	0.33	0.26	0.26	0.21	0.31
26–30	Female				0.18	0.26	0.25
	Male				0.20	0.30	0.45

*All correlations are significant $p<0.05$ except for those designated +, which are not significant.

age. For adults at 20 to 25 years (Figures 1*A*, 1*B*), there is little risk that adult levels will exceed the 90th percentile when childhood levels were less than the 50th percentile. For both genders, risk is progressively higher for elevated adult levels when childhood levels exceed the 50th percentile of total cholesterol. For those with childhood levels at the 90th percentile, risk for high adult levels ranges from 24% (95% confidence interval 17% to 32%) to 32% (confidence interval 20% to 47%). Similar relationships are shown between childhood levels and adult levels at ages 26 to 30 years (Figures 1*C*, 1*D*).

Predictive value of childhood cholesterol levels. Figure 2 shows the adult predictive value of an elevated childhood cholesterol level by age of childhood sampling. For the purposes of this presentation, childhood elevated


A
AGE (yrs)
9-10
11-12
13-14
15-16
17-18
RISK
MALES
CHOLESTEROL PERCENTILE


B
AGE (yrs)
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17-18
RISK
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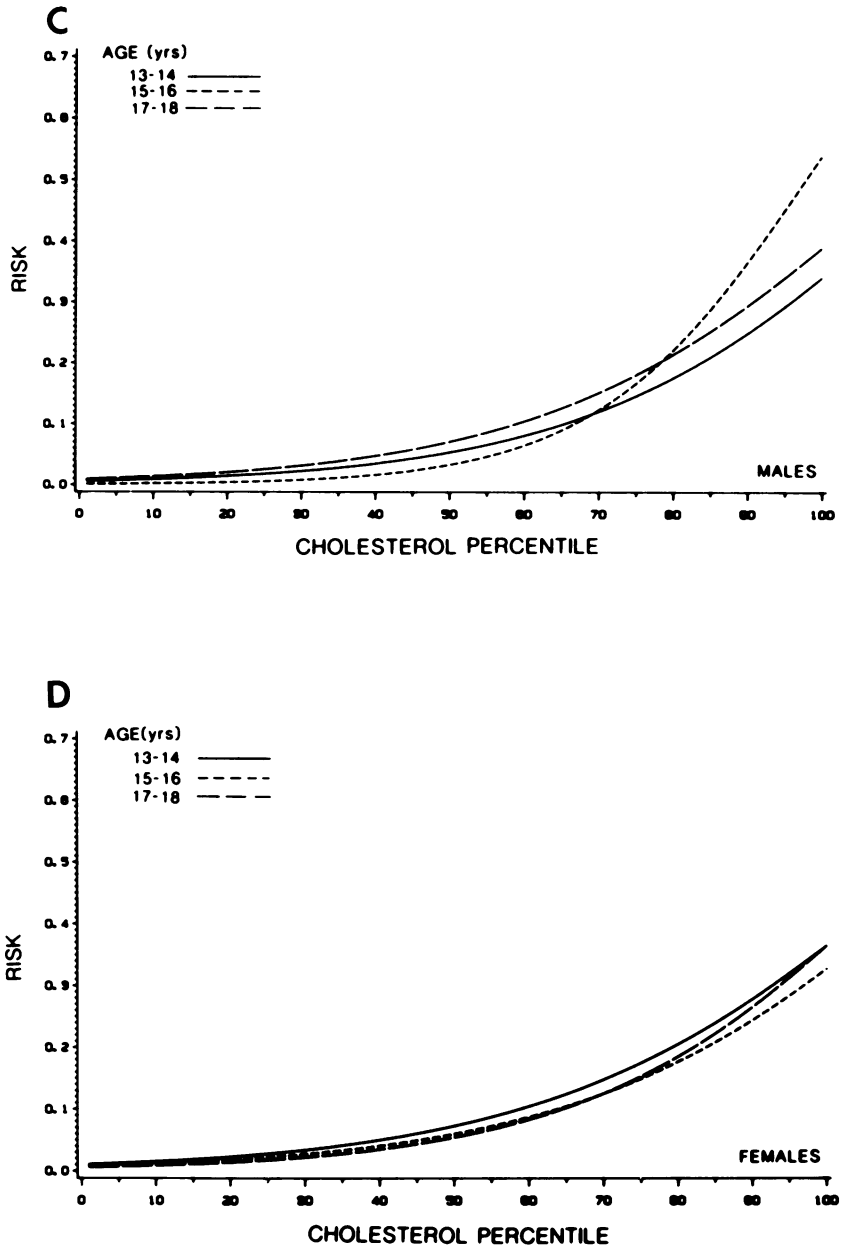

Fig. 1A,B,C,D. Risk of plasma cholesterol levels to be greater than or equal to the 90th percentile at 20 to 25 years in men (A) and women (B), and at 26 to 30 years of age in men (C) and women (D).

cholesterol is defined as a level greater than or equal to the 90th percentile for the age-gender specific group. Elevated adult cholesterol levels are defined as greater than or equal to the 75th percentile for the age-gender specific group. The 75th percentile was selected as the cut point in adults because the National Cholesterol Education Program has suggested that adults with levels exceeding the 75th percentile and at least two other coronary risk factors be offered dietary intervention, with drug therapy if severely elevated.[17] Note that of children whose cholesterol levels exceed the 90th percentile, 50–87% are above the 75th percentile as adults with highest values noted in the oldest adolescent group over the shortest period of observation. Of children whose cholesterol levels are less than the 90th percentile, 78–84% are below the 75th percentile as adults.

Relationships of other factors to adult cholesterol levels. The stepwise regression analyses predicting adult cholesterol from childhood cholesterol, change in Quetelet Index, and adult oral contraceptive use are shown in Figure 3 (3A males and 3B females). This shows that initial childhood cholesterol is the major predictor for adult level, but that the change in Quetelet Index adds significantly to the explained variance in both genders, and that adult oral contraceptive use adds significantly to female predictions.

The relationship of cholesterol and its fractions to reported smoking habits and alcohol use is shown in Table IV. Drinking an alcohol-containing beverage at least once per week was associated with a higher HDL-cholesterol and lower LDL/HDL ratios. One or more packs of cigarettes a day was associated with lower HDL-cholesterol and higher LDL/HDL ratios. No consistent associations between the subjects' reported exercise habits and their lipids and lipoprotein fractions were observed, and these data are not presented.

Table V shows that oral contraceptive use in females was associated with significantly higher total cholesterol, LDL-cholesterol levels and LDL/HDL ratios, while no difference was seen between users and nonusers of oral contraceptives with respect to HDL-cholesterol. These differences were not explained by a confounding of smoking with oral contraceptive use.

The relationship of a family history to cholesterol and its fractions is presented in Table VI. A family history of high cholesterol levels was associated with higher total and LDL-cholesterol and higher LDL/HDL ratios but no significant difference in HDL-cholesterol in the young adults. A family history of myocardial infarction was associated with a higher total cholesterol and LDL-cholesterol in 20-to-30-year-old men and also approached significance in women. A family history of diabetes was not related to lipid levels. Stroke was very infrequent in the relatives of this population and thus is not reported.

TABLE IV. COMPARISONS OF ADULT (20–30 YEARS) TOTAL, LDL AND HDL CHOLESTEROL AND LDL/HDL RATIO BY ALCOHOL AND CIGARETTE USE

	Number		*Cholesterol*		*LDL-cholesterol*		*HDL-cholesterol*		*LDL/HDL Ratio*	
	Female	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*
					Means by alcohol use					
Do not use	137	82	166.2	170.5	98.5	107.5	49.4	39.4	2.2	2.9
Not weekly	665	730	169.5	171.2	104.3	109.2	47.5	40.8	2.4	2.8
Weekly	424	325	171.0	171.2	101.2	105.4	53.9	45.4	2.0	2.5
p			0.332	0.981	0.009	0.148	0.001	0.001	0.001	0.001
Pooled st. dev.			33.2	32.3	30.2	28.9	11.9	10.5	1.0	1.0
					Means by cigarette use					
Exsmoker	102	104	164.5	175.5	97.9	106.2	50.4	45.5	2.0	2.5
Nonsmoker	736	608	169.1	169.4	100.2	105.2	51.7	44.4	2.1	2.5
<0.5 pack/day	133	118	169.0	171.6	100.3	107.4	50.3	43.8	2.2	2.6
0.5–1 pack/day	173	172	171.3	173.1	106.0	108.6	45.5	42.0	2.5	2.8
>1 pack/day	77	128	177.4	173.6	115.2	110.6	41.5	41.4	3.1	2.9
p			0.120	0.275	0.001	0.311	0.001	0.004	0.001	0.000
Pooled st. dev.			33.1	32.2	30.0	28.9	11.9	10.7	1.0	1.0

Means connected by brackets are not significantly different from each other by Tukey's Multiple Comparison Procedure.

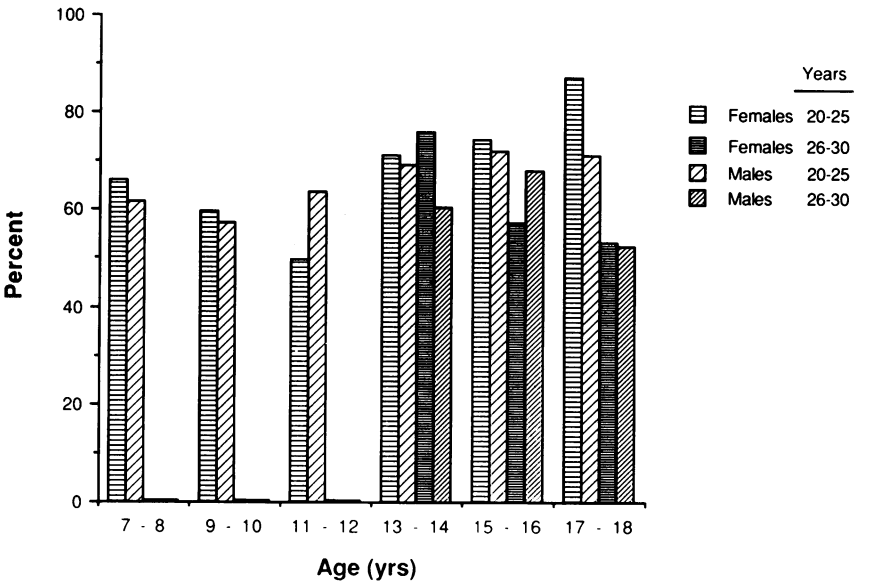

Fig. 2. Adult predictive value of an elevated childhood cholesterol level by age of childhood sampling. Elevated cholesterol in childhood is defined as greater than or equal to the 90th percentile for age and gender. Prediction (percent) is for adult levels greater than or equal to the 75th percentile.

The stepwise regression analyses predicting adult cholesterol levels and its fractions is presented in Table VII. These analyses show that adult Quetelet Index, cigarette smoking, and contraceptive use are associated with adverse levels of cholesterol, LDL-cholesterol, and HDL-cholesterol. Alcohol use results in a slight increase in HDL levels. Overall, 13 to 18% of the variability of the LDL/HDL cholesterol ratio is explained by these four factors.

DISCUSSION

This study of a population of children followed into adult life shows that cholesterol measurements obtained in childhood are predictive of adult levels of total and LDL-cholesterol, with 25 to 50% of adult cholesterol variability explained by childhood levels. Of children with cholesterol levels initially greater than the 90th percentile on at least one measurement, on average for ages seven–18 years, 43% were found to have levels greater than 90th percentile at ages 20 to 30 years, with 62% greater than 75th percentile and 81% greater than 50th percentile at the adult ages. LDL-cholesterol and HDL-cholesterol levels and their ratio were affected by a number of acquired lifestyles, including the development of obesity, cigarette smoking, alcohol,

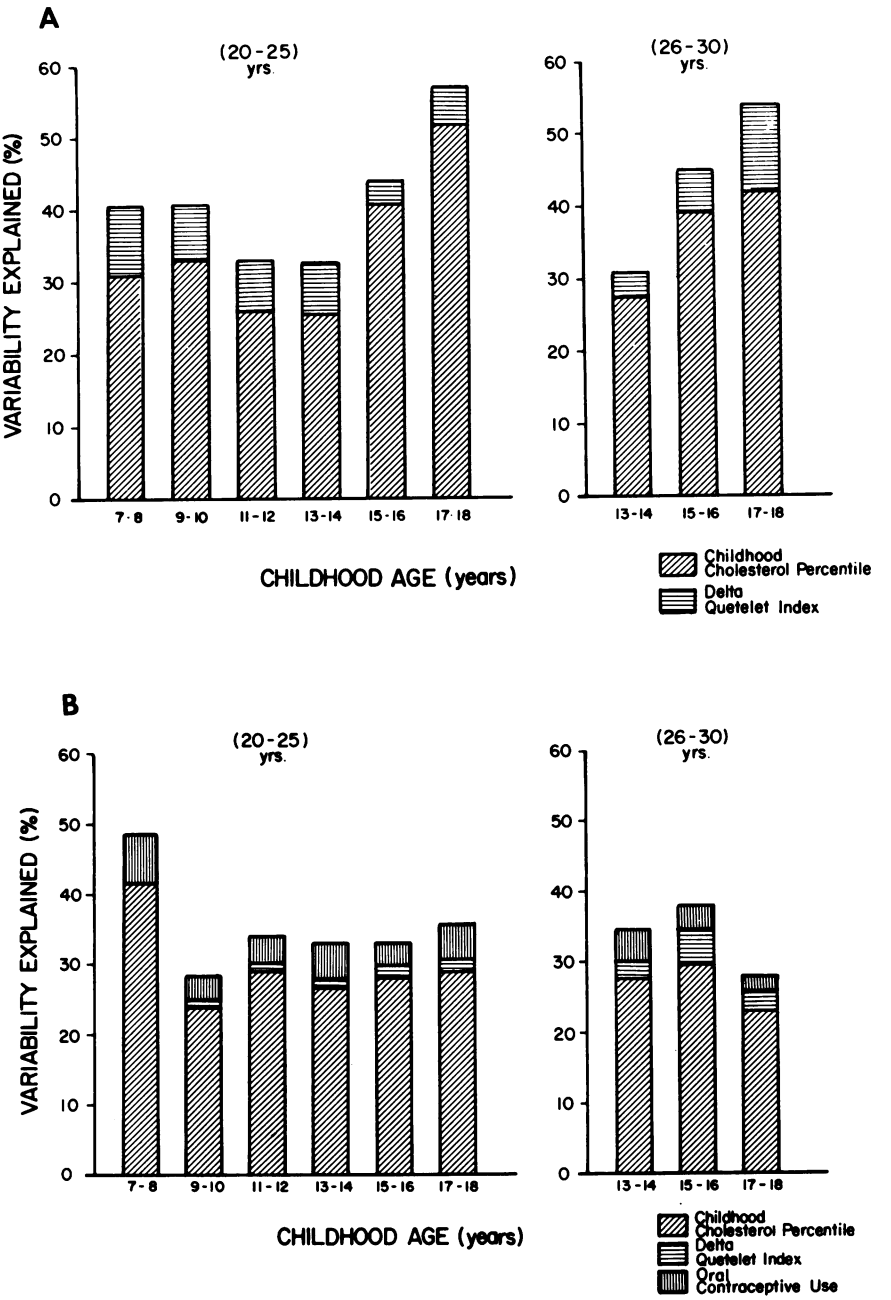

Fig. 3. Percentage of cholesterol variability at 20 to 25 years and 26 to 30 years explained by childhood cholesterol, change in Quetelet index, and adult oral contraceptive use by age at childhood observation in men (A) and women (B).

TABLE V. COMPARISON OF ADULT (20–30 YEARS) TOTAL, LDL AND HDL CHOLESTEROL AND LDL/HDL RATIO BY ORAL CONTRACEPTIVE USE IN FEMALES

Oral contraceptive use	*Cholesterol*		*LDL*		*HDL*		*LDL/HDL ratio*	
	No	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*
Mean	164.8	178.2	99.4	106.3	49.5	50.6	2.2	2.3
Standard deviation	32.0	33.4	29.3	31.5	12.2	12.4	0.9	1.1
Number	781	446						
p	0.0001		0.0001		0.165		0.049	

TABLE VI. COMPARISON OF ADULT (20–30 YEARS) TOTAL, LDL AND HDL CHOLESTEROL AND LDL/HDL RATIO BY FAMILY HISTORY OF HIGH CHOLESTEROL AND MYOCARDIAL INFARCTION

	Cholesterol		*LDL*		*HDL*		*LDL/HDL ratio*	
	No	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*
	Family history of high cholesterol in males							
Mean	169.1	180.4	104.8	115.2	43.8	43.1	2.3	2.8
Standard deviation	30.6	38.0	27.2	35.1	10.8	10.5	0.9	1.2
N	936	201	930	200	931	200	930	200
p	0.001		0.001		0.407		0.001	
	Family history of high cholesterol in females							
Mean	167.7	176.1	100.1	107.9	50.1	49.3	2.2	2.4
Standard deviation	32.4	35.1	29.6	31.8	12.4	12.0	1.0	1.1
N	947	280	932	279	934	279	932	279
p	0.001		0.001		0.333		0.005	
	Family history of myocardial infarction in males							
Mean	169.6	179.8	105.3	114.0	43.7	43.7	2.6	2.8
Standard deviation	31.8	33.7	28.5	30.5	10.8	10.8	1.0	1.2
N	963	174	959	171	960	171	959	171
p	0.001		0.001		0.962		0.011	
	Family history of myocardial infarction in females							
Mean	168.9	173.2	101.2	105.4	50.0	49.3	2.2	2.3
Standard deviation	32.8	34.6	30.1	31.1	12.4	12.0	1.0	1.1
N	1019	208	1005	206	1006	207	1005	206
p	0.089		0.068		0.408		0.106	

and oral contraceptive use. In addition, a family history of ischemic heart disease was an important correlate of elevated cholesterol levels in both children and adults, which suggests that heritable factors play an important role in the control of cholesterol levels.

Since the major predictor during childhood of adult cholesterol level is cholesterol itself, it suggests that factors resulting in high adult cholesterol levels begin at an early age. Children with high cholesterol often have parents with high cholesterol levels, and these families are at particularly high risk for

TABLE VII. PERCENT OF VARIABILITY OF ADULT LIPID LEVELS EXPLAINED BY ADULT QUETELET INDEX, TOBACCO, ALCOHOL AND ORAL CONTRACEPTIVE USE

Total cholesterol	*Contribution to regression (%)*			
	Females	*Females*	*Males*	*Males*
Age (years)	*10–25*	*26–30*	*20–25*	*26–30*
Quetelet index	—	—	7.99	4.43
Tobacco use	—	—	—	—
Alcohol use	—	—	—	—
Oral contraceptive use	7.21	4.24	—	—
Total	7.21	4.24	7.99	4.43
HDL-cholesterol				
Quetelet index	6.03	7.93	6.82	8.16
Tobacco use	8.40	3.33	1.72	2.74
Alcohol use	2.26	4.41	5.88	3.24
Oral contraceptive use	—	—	—	—
Total	16.69	15.67	14.42	14.14
LDL-cholesterol				
Quetelet index	—	3.53	6.19	3.45
Tobacco use	1.39	—	—	—
Alcohol use	0.70	—	—	—
Oral contraceptive use	2.23	2.58	—	—
Total	4.32	6.11	6.19	3.45
LDL/HDL ratios				
Quetelet index	4.43	9.05	12.98	8.88
Tobacco use	7.20	2.12	1.93	1.93
Alcohol use	2.06	3.25	3.51	1.85
Oral contraceptive use	—	1.50	—	—
Total	13.69	15.92	18.42	12.66

Note: Other variables used in regression included triceps skinfold, SES and exercise did not add to the prediction.

premature coronary heart disease.[18] The adverse effects of high childhood cholesterol are also suggested by the observation in childhood of increased fatty streaks covering the vascular surface in children with elevated LDL-cholesterol levels.[19] The frequency with which these fatty streaks persist and progress to occlusive disease in adult life is still an important unanswered question under active investigation.

As children mature, lifestyles related to caloric intake, exercise, cigarette smoking, the use of alcohol and oral contraceptives affect cholesterol and lipoprotein fractions in important ways. These lifestyle selections are often acquired during adolescence as indicated by the fact that obesity acquired in childhood is highly predictive of obesity in adult life;[20,21] smoking habits are often established by the beginning of high school;[22] dietary preferences for

foods rich in saturated fats are determined by cultural and social practice;[23] and regular oral contraceptive use frequently begins by age 15 years.[24] The deleterious effects of oral contraceptives on lipid levels in adolescence has also been reported by the Lipid Research Clinic Study.[25]

The mean level of serum cholesterol during childhood in the United States is significantly higher than in countries with lower coronary heart disease rates and where less saturated fat is consumed.[26] This suggests that dietary practices in United States children contribute to the evolving arteriosclerotic process. It has been suggested that lowering the distribution of childhood cholesterol levels by dietary change could improve adult coronary heart disease risk in the United States.[27] Whether such practices can be effectively adopted by children in the United States has yet to be determined, but several expert nutrition panels have concluded that they should attempt to do so.[28,29] This is supported by the Lipid Research Clinic's Coronary Primary Prevention Trial in young men which indicated that lowering blood cholesterol levels, albeit primarily by the use of bile acid sequestrants, has important protective effects against coronary heart disease.[7]

Children whose parents have early myocardial infarctions often have high cholesterol levels themselves. The measurement of cholesterol levels in children with a family history of angina pectoris or myocardial infarction before the age of 55 years is effective, 23% of such children having LDL-cholesterol levels greater than the 90th percentile.[30] Excessive caloric intake, lack of lack of exercise, cigarette smoking, and the use of oral contraceptives may affect cholesterol and its fractions in adverse ways. Cigarette smoking is particularly deleterious for those who may need to use oral contraceptives.[31,32] While alcohol consumption does improve HDL levels and coronary heart disease, it is an important risk factor for automobile deaths, hypertension, liver disease, and breast cancer. Thus, the use of alcohol as an adjunct to nutrition to generate higher HDL-cholesterol levels is a practice that requires careful consideration.

For a health screening program to be effective, the disease to be screened should have a high prevalence and an effective form of therapy. Data presented herein suggests that although high cholesterol levels in childhood is the major predictor of adult high cholesterol levels, there is considerable variability and only 62% of children with cholesterol levels greater than or equal to the 90th percentile remain above the 75th percentile level as adults. Since a single high cholesterol measurement has this variability, and since the costs, risks, and effectiveness of intervention for high cholesterol in childhood have not been established, mass screening of cholesterol in children should be considered carefully.

SUMMARY

2,446 subjects initially examined at ages eight to 18 years were reexamined as young adults at ages 20–25 years or 26–30 years. Measurements of cholesterol, height, weight, and triceps skinfold thickness were obtained during childhood. Lipids, lipoprotein fractions, family history as well as medication, alcohol,and tobacco use were determined during the adult examination. Elevated levels of cholesterol during childhood were associated with elevation in adult life. On average, of children found to have cholesterol levels greater than or equal to the 90th percentile for their age and gender, on a single measurement 43% remained above the 90th percentile, 62% remained above the 75th percentile, and 81% remained above the 50th percentile. Obesity acquired in adolescence and the young adult years, oral contraceptive use, and cigarette smoking had deleterious effects upon adult cholesterol levels and lipoprotein fractions.

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